Efficacy and safety outcomes of emerging EGFR-TKIs for patients with non-small cell lung cancer with EGFR exon 20 insertion mutations: A systematic review and meta-analysis

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Abstract. Lung cancer remains a leading cause of mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for ~85% of all lung cancer cases. Epidermal growth factor receptor (EGFR) exon 20 insertion mutant NSCLC is rare and associated with poor outcomes. Several novel generations (third-generation) of EGFR-tyrosine kinase inhibitors (TKIs) have been developed for the treatment of NSCLC and have shown antitumour potential. Therefore, the present study reviewed their efficacy and safety outcomes for this condition. A thorough literature searching was performed using the Cochrane Library, Web of Science, PubMed and Embase databases. Clinical trials published in English and reporting overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and treatment relevant adverse events (TRAEs) of grade ≥3 were included for further analysis. A total of 13 studies were included. All included studies reported ORRs with a pooled ORR of 0.486 [95% confidence interval (CI), 0.369-0.602]. Subgroup analysis revealed the following ORRs: 0.731 (95% CI, 0.560-0.901; I^2=0%) for YK-029A; 0.608 (95% CI, 0.511-0.705; I^2=0%) for sunvozertinib; 0.602 (95% CI, 0.440-0.764; I^2=80.2%) for furmonertinib; 0.602 (95% CI, 0.486-0.718; I^2=84.5%) for befotertinib; 0.566 (95% CI, 0.236-0.896; I^2=96.3%) for amivantamab; 0.444 (95% CI, 0.215-0.674; I^2=0%) for BEBT-109; and 0.256 (95% CI, 0.178-0.334; I^2=75.0%) for poziotinib. The pooled DCR, median PFS and median OS were 0.843 (95% CI, 0.740-0.946), 10.11 months (95% CI, 9.58-10.64 months; I^2=78.8%; P<0.001) and 23.00 months (95% CI, 20.30-25.69 months; I^2=44.8; P=0.178), respectively. The pooled incidence of TRAEs of grade ≥3 was 0.458 (95% CI, 0.336-0.580; I^2=96.9%; P<0.001), with the incidence of the three most reported TRAEs (diarrhoea, thrombocytopenia and anaemia) demonstrated to be 0.112 (95% CI, 0.060-0.164), 0.065 (95% CI, -0.012-0.141) and 0.040 (95% CI, 0.005-0.076), respectively. In conclusion, the emerging EGFR-TKIs for NSCLC with EGFR exon 20 insertion have a promising treatment outcome with a manageable safety profile. However, further analysis is needed when more clinical data are released.

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Introduction

Lung cancer remains a leading cause of mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for ~85% of all lung cancer cases (1). Over the past decades, notable advancements have been made in understanding the molecular biology of NSCLC, particularly the identification of key driver mutations such as those in the epidermal growth factor receptor (EGFR) gene (2). Historically, research breakthroughs in the early 2000s led to the development of targeted therapies, beginning with first-generation EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib, which showed marked efficacy in treating patients with common EGFR mutations, such as exon 19 in-frame deletion and exon 21 L858R alterations substitutions (3,4). However, rarer EGFR mutations, such as EGFR exon 20 insertions, which represent 4-10% of EGFR mutations in NSCLC, have proven more resistant to these therapies, leading to worse clinical outcomes (5,6). These mutations exhibit inherent resistance to first- and second-generation EGFR-TKIs, and even third-generation inhibitors such as osimertinib, which have been effective in overcoming resistance to earlier drugs, have shown limited success in addressing exon 20 insertions in clinical trials (7).

Therefore, newer EGFR-TKIs have been developed to target this unique mutation profile. Mobocertinib (also known as TAK-788) is an oral EGFR-TKI and was the first and only agent approved globally for the treatment of advanced exon 20 insertion mutant NSCLC. Early clinical trials reported that treatment with 160 mg mobocertinib once daily was associated

with an overall response rate (ORR) of 28%, a disease control rate (DCR) of 78%, a mean progression-free survival (PFS) of 7.3 months and an overall survival (OS) of 20.2 months (8-10). However, it did not reach the primary endpoint in the phase III study, although no new safety signals were observed. Thus, the U.S. Food and Drug Administration (FDA) and Takeda, the sponsor of mobocertinib, voluntarily withdrew the drug for the indicated patients in October 2023 (11).

Nevertheless, emerging medications such as sunvozertinib (DZD9008) and furmonertinib (AST2818) are potential candidates as they have been reported to inhibit EGFR exon 20 insertion mutations with an acceptable safety profile in initial studies (12,13). However, as the comprehensive data on the efficacy and safety of these emerging drugs in treating patients with NSCLC with EGFR exon 20 insertions are still lacking, the present study aimed to perform a systematic review and meta-analysis to evaluate the efficacy and safety outcomes of the key emerging EGFR-TKIs, namely sunvozertinib, furmonertinib, poziotinib, amivantamab, zipalertinib, befotertinib, YK-029A, BEBT-109 and BLU-451, for the treatment of patients with NSCLC with EGFR exon 20 insertion mutations.

Materials and methods

Protocol. The present systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (14). The present review protocol was registered in the PROSPERO database (registration ID no. CRD42023472851).

Search strategy and criteria. A total of four databases [the Cochrane Library (https://www.cochranelibrary.com/), Web of Science (https://www.webofscience.com/wos/), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Embase (https://www.embase.com/)] were used for relevant literature searches due to their comprehensive coverage of biomedical literature and their relevance to oncology research. The main search items to refine the search included 'EGFR-TKIs', 'Zipalertinib', 'Sunvozertinib', 'Furmonertinib', 'Poziotinib', 'Amivantamab', 'Befotertinib', 'YK-029A', 'BEBT-109', 'BLU-451', 'NSCLC' and 'EGFR exon 20 insertions'. The search covered the period from September 2019 to the study conduction date, April 2024, representing a timeframe during which third-generation EGFR-TKIs emerged as promising candidates in clinical trials. The April 2024 endpoint represents the intended cut-off for data collection at the time of planning the present meta-analysis. Whilst no additional data were included beyond the actual completion of the present study, this timeframe ensured a comprehensive review of relevant clinical trials within the predefined scope. Detailed search queries were tailored for each database, considering their specific search algorithms and indexing practices (Table I).

Studies were included if the following inclusion criteria were met: i) Population: Patients had a confirmed diagnosis of EGFR exon 20 insertion mutation- or T790M mutation-positive NSCLC; ii) intervention: Patients were treated with third-generation EGFR-TKIs including zipalertinib, sunvozertinib, furmonertinib, poziotinib, amivantamab, befotertinib, YK-029A, BEBT-109 and BLU-451. Mobocertinib was not included as its further development program was withdrawn due to the FDA withdrawal (11); iii) study type: Clinical trials published in English, including randomised controlled trials and single arm prospective trials, and sub-group analyses of previously published studies; and iv) outcomes: Clinical tumour outcomes including ORR, DCR, PFS, OS and treatment relevant adverse events (TRAEs) of grade ≥3. The tumour response was evaluated using the Response Evaluation Criteria in Solid Tumours version 1.1 (15). Safety concerns were assessed for their incidence and severity using the Common Terminology Criteria for Adverse Events (16). The exclusion criteria were as follows: i) Studies focusing exclusively on osimertinib, as it is an established treatment and not the primary focus of the present review; ii) preclinical or animal studies; iii) case reports, reviews, editorials or other non-original research articles. Systematic reviews and meta-analysis were only used for reference cross-checking; and iv) publications not available in English.

Data extraction and quality assessment. A total of two investigators independently extracted all required data for the included studies and subsequently performed the quality assessment of the studies. The extracted data included the authors, year of publication, study phase and registration number, sample size, interventions and reported outcomes. Efficacy outcomes included ORR, DCR, PFS and OS. The safety outcome was the incidence of TRAEs of grade ≥3. The Newcastle Ottawa Scale (NOS) was used to evaluate the quality of prospective cohort studies and indirect comparison studies (17).

Meta-analysis. All data in the present meta-analysis were analysed using STATA 17.0 software (StataCorp LP). Heterogeneity was measured using the χ^2 test and I^2 statistic. $P<0.05$ was considered to indicate a statistically significant difference. As a random-effects model accounts for variability between studies in a more flexible and comprehensive way than a fixed-effects model, a random-effects model was performed in the present study. Disease-free survival (DFS) was collected as a continuous variable and ultimately consolidated into a single DFS group, presented as the median with its 95% confidence interval (CI). Several studies reported the confirmed ORR and they were analysed as the ORR in the present meta-analysis. Funnel plots and Egger's test were used to quantitatively analyse publication bias (18,19).

Results

Literature selection and study characteristics. The search across the PubMed, Cochrane Library, Embase and Web of Science databases yielded a total of 314 articles. After initial screening, 190 were excluded due to duplicates or irrelevance, leaving 124 articles eligible for full-text review. Following a rigorous evaluation, 13 studies were ultimately included in the systematic review and meta-analysis (13,20-31) (Fig. 1). The included studies were published between 2021 and 2024 and encompassed a total of 1,642 patients diagnosed with NSCLC with EGFR exon 20 insertion mutations. The characteristics of the selected studies are summarized in Table II. The included studies mainly consisted of Phase II

Table I. Detailed search queries used for the literature search.

Database	Search strategy	Records, n
PubMed	#((‘EGFR-tyrosine kinase inhibitor’[All Fields] OR ‘EGFR-TKI’[All Fields] OR ‘Zipalertinib’ [All Fields] OR ‘Sunvozertinib’[All Fields] OR ‘Furmonertinib’[All Fields] OR ‘Poziotinib’ [All Fields] OR ‘Amivantamab’[All Fields] OR ‘Befotertinib’[All Fields]) OR ‘YK-029A’ [All Fields]) OR ‘BEBT-109’[All Fields]) OR ‘BLU-451’[All Fields]) AND (‘Non-small cell lung cancer’[All Fields] OR ‘NSCLC’[All Fields]) AND ‘exon 20’[All Fields] AND (‘clinical trial’[Publication Type] OR ‘randomized controlled trial’[Publication Type])) AND ((y_5[Filter]) AND (clinicaltrial[Filter] OR randomized controlled trial[Filter]))#	15
Cochrane	#(‘EGFR tyrosine kinase inhibitor’ OR ‘EGFR-TKI’ OR ‘Zipalertinib’ OR ‘Sunvozertinib’ OR ‘Furmonertinib’ OR ‘Poziotinib’ OR ‘Amivantamab’ OR ‘Befotertinib’ OR ‘YK-029A’ OR ‘BEBT-109’ OR ‘BLU-451’):ti,ab,kw AND ((‘Non-small cell lung cancer’ OR ‘NSCLC’) AND (‘exon 20’)):ti,ab,kw AND English:la (Word variations have been searched) with Publication Year from 2019 to 2024, with Cochrane Library publication date Between Sep 2019 and Apr 2024, in Trials (Word variations have been searched)#	61
Embase	#(‘egfr-tyrosine kinase inhibitor’ OR ‘egfr-tki’ OR ‘Zipalertinib’/exp OR ‘Sunvozertinib’ OR ‘Furmonertinib’/exp OR ‘Poziotinib’ OR ‘Amivantamab’/exp OR ‘Befotertinib’ OR ‘YK-029A’/exp OR ‘BEBT-109’/exp OR ‘BLU-451’) AND (‘non-small cell lung cancer’/exp OR ‘non-small cell lung cancer’ OR ‘nsclc’) AND (‘exon 20’/exp OR ‘exon 20’) AND (2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py) AND (‘clinical article’/de OR ‘clinical study’/de OR ‘clinical trial’/de OR ‘clinical trial topic’/de OR ‘cohort analysis’/de OR ‘comparative effectiveness’/de OR ‘comparative study’/de OR ‘controlled clinical trial’/de OR ‘controlled study’/de OR ‘major clinical study’/de OR ‘observational study’/de OR ‘phase 1 clinical trial’/de OR ‘phase 1 clinical trial topic’/de OR ‘phase 2 clinical trial’/de OR ‘phase 2 clinical trial topic’/de OR ‘phase 3 clinical trial’/de OR ‘phase 3 clinical trial topic’/de OR ‘prospective study’/de OR ‘randomized controlled trial’/de OR ‘randomized controlled trial topic’/de) AND (‘article’/it OR ‘article in press’/it) AND (‘case control study’/de OR ‘clinical trial’/de OR ‘comparative effectiveness’/de OR ‘comparative study’/de OR ‘controlled clinical trial’/de OR ‘controlled study’/de OR ‘longitudinal study’/de OR ‘major clinical study’/de OR ‘multicenter study’/de OR ‘observational study’/de OR ‘phase 1 clinical trial’/de OR ‘phase 2 clinical trial’/de OR ‘phase 3 clinical trial’/de OR ‘prospective study’/de OR ‘randomized controlled trial topic’/de OR ‘retrospective study’/de)#	74
Web of Science	#((((ALL=(‘EGFR tyrosine kinase inhibitor’ OR ‘EGFR-TKI’ OR ‘Zipalertinib’ OR ‘Sunvozertinib’ OR ‘Furmonertinib’ OR ‘Poziotinib’ OR ‘Amivantamab’ OR ‘Befotertinib’ OR ‘YK-029A’ OR ‘BEBT-109’ OR ‘BLU-451’)) AND ALL=((‘Non-small cell lung cancer’ OR ‘NSCLC’) AND ‘exon 20’)) AND LA=(English)) AND DOP=(2019-09-01/2024-04-1)) AND DT=(Article)#	76

trials (13,22,24-28), accounting for 7/13 (53.8%), followed by Phase I trials (20,23,30,31), accounting for 4/13 (30.8%). The study design included 12 single arm studies and one randomized controlled trial; however, only the results of amivantamab were extracted from this randomized controlled trial. Most of the included literature reported PFS (13,20,23,28,29), but due to insufficient follow-up time, only 3 articles reported OS (20,22,28). No efficacy or safety data on zipalertinib or BLU-451 were reported.

Quality assessment. To maintain the integrity and reliability of the findings, the risk-of-bias of each study was assessed. The NOS was used to evaluate the quality of prospective cohort studies and indirect comparison studies. Each study scored above six on the nine-point system, thereby indicating moderate-to-high quality. The quality assessment details are presented in Table III.

Tumour response. All studies included in the present analysis reported the ORR for the assessed EGFR-TKIs for patients with NSCLC with exon 20 insertions, which ranged from 14.7-74.1%. The meta-analysis results revealed significant heterogeneity among all studies (I^2=96.2%; P<0.001); therefore, a random effects model was used for analysis, with a combined ORR of 0.486 (95% CI, 0.369-0.602; Fig. 2). Subgroup analysis was performed on the drugs used in each study, and a total of seven drugs were included. According to the size of ORR, they were YK-029A (ORR, 0.731; 95% CI, 0.560-0.901; I^2=0%), sunvozertinib (ORR, 0.608; 95% CI, 0.511-0.705; I^2=0%), furmonertinib (ORR, 0.602; 95% CI, 0.440-0.764; I^2=80.2%), befotertinib (ORR, 0.602; 95% CI, 0.486-0.718; I^2=84.5%), amivantamab (ORR, 0.566; 95% CI, 0.236-0.896; I^2=96.3%), BEBT-109 (ORR, 0.444; 95% CI, 0.215-0.674; I^2=0%) and poziotinib (ORR, 0.256; 95% CI, 0.178-0.334; I^2=75.0%).

Table II. Characteristics of clinical studies of patients with non-small cell lung cancer with EGFR exon 20 insertions using emerging third-generation EGFR-tyrosine kinase inhibitors.

First author/s, year	Phase	Registration no.	Study design	Intervention	Sample size	ORR, %	Median PFS, months (95% CI)	Median OS, months (95% CI)	(Refs.)
Park *et al*, 2021	I	NCT02609776	Single arm	Amivantamab	81	40	8.3 (6.5-10.9)	22.8 (14.6-not reached)	(20)
Girard *et al*, 2023	III	NCT04538664	RCT	Amivantamab	153	73	11.4 (9.8-13.7)	NR	(21)
Lu *et al*, 2022	II	NCT04206072	Single arm	Befotertinib 50 mg/day	176	54	11.0 (9.6-12.5)	23.9 (21.1-27.1)	(22)
				Befotertinib 100 mg/day	290	65.9	12.5 (11.1-13.8)	NR	
Shi *et al*, 2021	II	NCT03452592	Single arm	Furmonertinib	220	74.1	9.6 (8.2-9.7)	NR	(13)
Zeng *et al*, 2024	I	CTR20192575	Single arm	BEBT-109	18	44.4	8.3 (1.3-14.7)	NR	(23)
Wang *et al*, 2024	II	NCT05712902	Single arm	Sunvozertinib	97	61	9.7	NR	(24)
Le *et al*, 2021	II	NCT03318939	Single arm	Poziotinib	95	14.7	NR	NR	(25)
Cornelissen *et al*, 2021	II	NCT03318939	Single arm	Poziotinib	205	20.5	NR	NR	(26)
Sacher *et al*, 2021	II	NCT03318939	Single arm	Poziotinib	79	27.8	7.2	NR	(27)
Elamin *et al*, 2022	II	NCT03066206	Single arm	Poziotinib	50	32.0	5.5 (5.4-10.4)	19.2 (11.8-24.1)	(28)
Piotrowska *et al*, 2023	I/II	NCT04036682	Single arm	Zipalertinib	73	38.4	10.0 (6.0-12.0)	NR	(29)
Duan *et al*, 2024	I	NCT05767866	Single arm	YK-029A	26	73.1	9.3	NR	(30)
Han *et al*, 2023	I	NCT04858958	Single arm	Furmonertinib treatment-naïve 240 mg/day	30	69.0	10.7	NR	(31)
				Furmonertinib previously treated 240 mg/day	24	50.0	7.0	NR	
				Furmonertinib previously treated 160 mg/day	25	40.9	5.8	NR	

NR, not reported; RCT, randomized controlled trial; PFS, progression-free survival; CI, confidence interval; ORR, overall response rate.

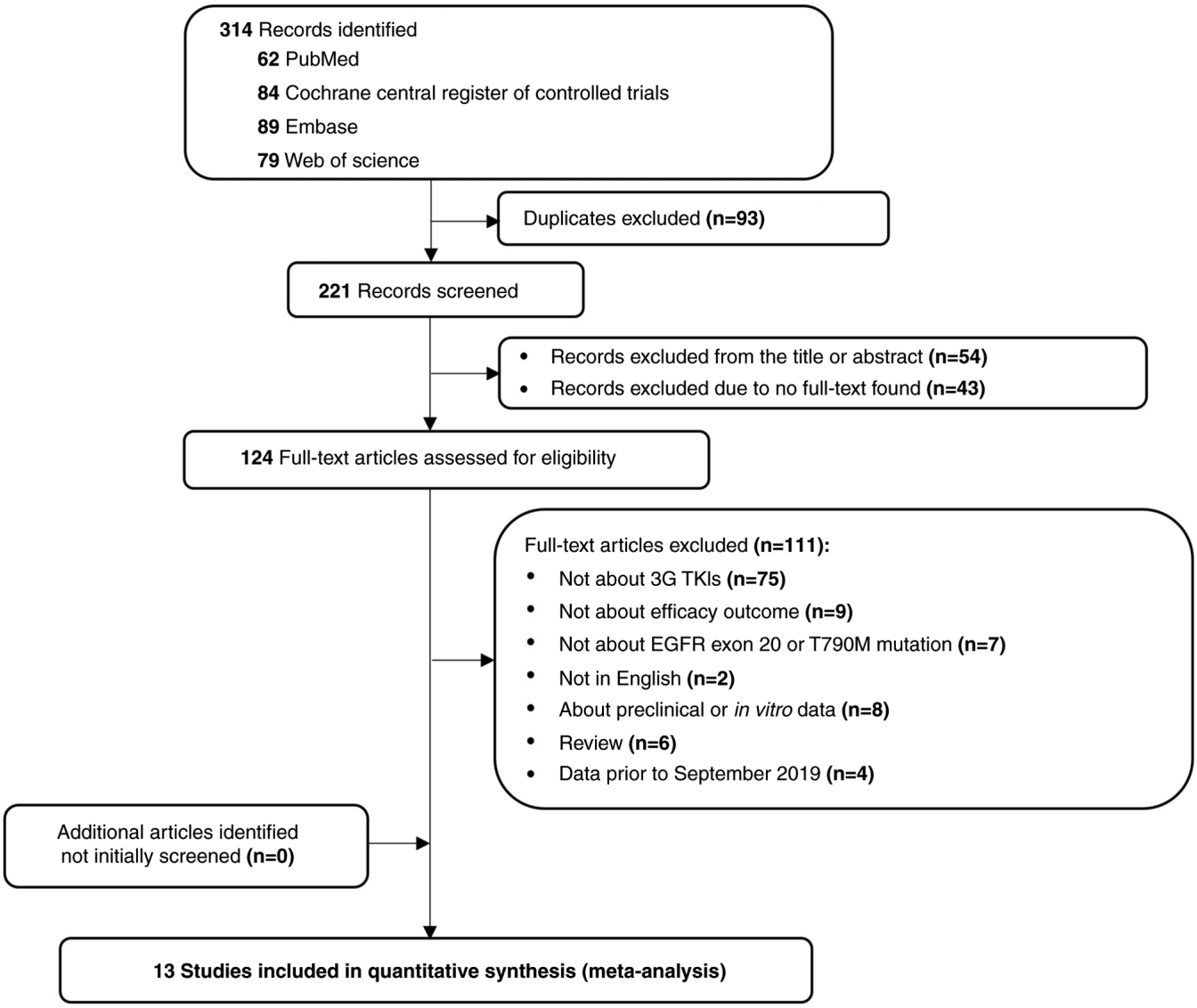

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. TKI, tyrosine kinase inhibitor.

A total of five studies reported the DCR (13,24,25,27,30), and a random effects model was used for analysis as there was significant heterogeneity between studies (I^2=91.7%; P<0.001). The merged DCR value was 0.843 (95% CI, 0.740-0.946; Fig. 3).

Survival. A total of 11 articles reported PFS (13,20,23,28,29), with 7 studies reporting its 95% CI. A total of three articles reported OS (20,22,28), whilst one of them reported OS not reached (20). Using the random-effects model, the pooled median PFS was 10.11 months (95% CI, 9.58-10.64 months; I^2=78.8%; P<0.001; Fig. 4). Using the random-effects model, the pooled median OS was 23.00 months (95% CI, 20.30-25.69 months; I^2=44.8; P=0.178; Fig. 5).

Safety. A total of 12 studies reported TRAEs of grade ≥3 (13,20-30), with the incidence varying from 15.0-84.0%. The three most reported TRAEs associated with the emerging EGFR-TKIs were diarrhoea, rash and hypokalaemia. Overall, the pooled incidence of TRAEs of grade ≥3 was 0.458 (95% CI, 0.336-0.580; I^2=96.9%; P<0.001; Fig. 6), with diarrhoea (0.112; 95% CI, 0.060-0.164) thrombocytopenia (0.065; 95% CI, -0.012-0.141) and anaemia (0.040; 95% CI, 0.005-0.076) the most commonly reported. Further details are presented in Table IV.

Publication bias. The number of studies included in the pooled ORR was 13. The Begg's funnel plot demonstrated an incomplete symmetrical scatter distribution (Fig. 7). Furthermore, Egger's test was used to quantitatively analyse publication bias, and the P-value was 0.844, indicating that there was no significant publication bias in the included literature.

Discussion

A total of 13 trials involving 9 investigational agents were included in the pooled analysis. The sample size was relatively small due to the early-stage development of these agents and the rigorous clinical trial process, which limited the availability of published data. The pooled analysis of these included

Table III. Quality assessment of the studies included in the meta-analysis.

	Selection of cohorts					Outcome				
First author/s, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	NOS score	(Refs.)
Park *et al*, 2021	1	0	1	1	1	1	1	1	7	(20)
Girard *et al*, 2023	1	0	1	1	1	1	1	1	7	(21)
Lu *et al*, 2022	1	1	1	1	2	1	1	1	9	(22)
Shi *et al*, 2021	1	0	1	1	1	1	1	1	7	(13)
Zeng *et al*, 2024	1	0	1	1	1	1	1	1	7	(23)
Wang *et al*, 2024	1	0	1	1	1	1	0	1	6	(24)
Le *et al*, 2021	1	0	1	1	1	1	0	1	6	(25)
Cornelissen *et al*, 2021	1	0	1	1	1	1	0	1	6	(26)
Sacher *et al*, 2021	1	0	1	1	1	1	0	1	6	(27)
Elamin *et al*, 2022	1	0	1	1	1	1	1	1	7	(28)
Piotrowska *et al*, 2023	1	0	1	1	1	1	1	1	7	(29)
Duan *et al*, 2024	1	0	1	1	1	1	0	1	6	(30)
Han *et al*, 2023	1	1	1	1	2	1	0	1	8	(31)

NOS, Newcastle Ottawa Scale; each item within the three domains (selection, comparability and outcome) is assigned a score of either 0 or 1.

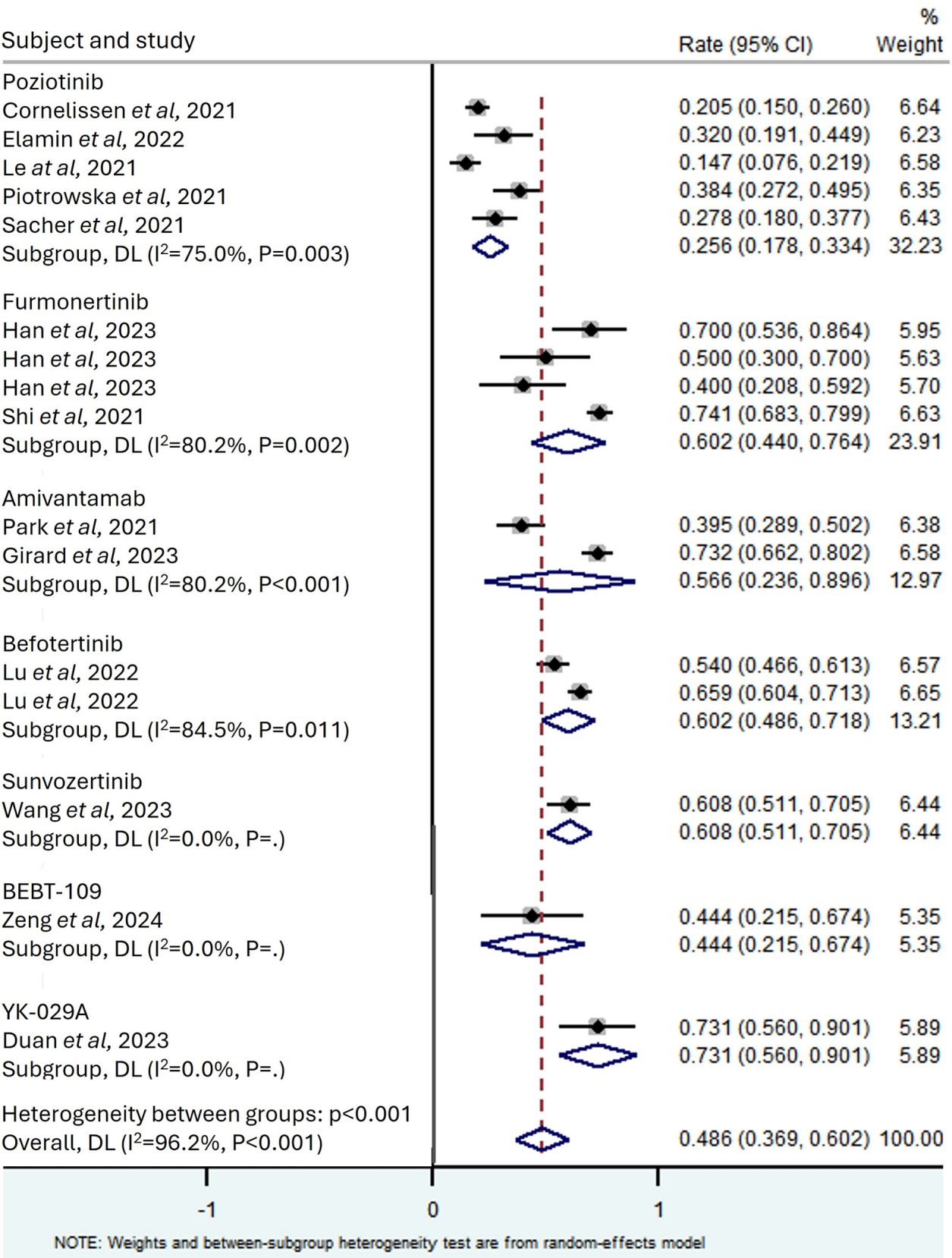

Figure 2. Forest plot of the pooled objective response rate. CI, confidence interval; DL, DerSimonian-Laird procedure.

emerging third-generation EGFR-TKIs demonstrated a pooled ORR of 48.6%, a median PFS of 10.11 months and a median OS of 23.00 months. Furthermore, a recently published real-world study reported confirmed ORRs of 14.0-18.6%, a median PFS of 11.5-17.0 months and a median OS of 3.3-5.2 months in patients with EGFR exon 20 insertion-mutant NSCLC (32). These findings suggest that the emerging third-generation EGFR-TKIs may offer good treatment outcomes for this

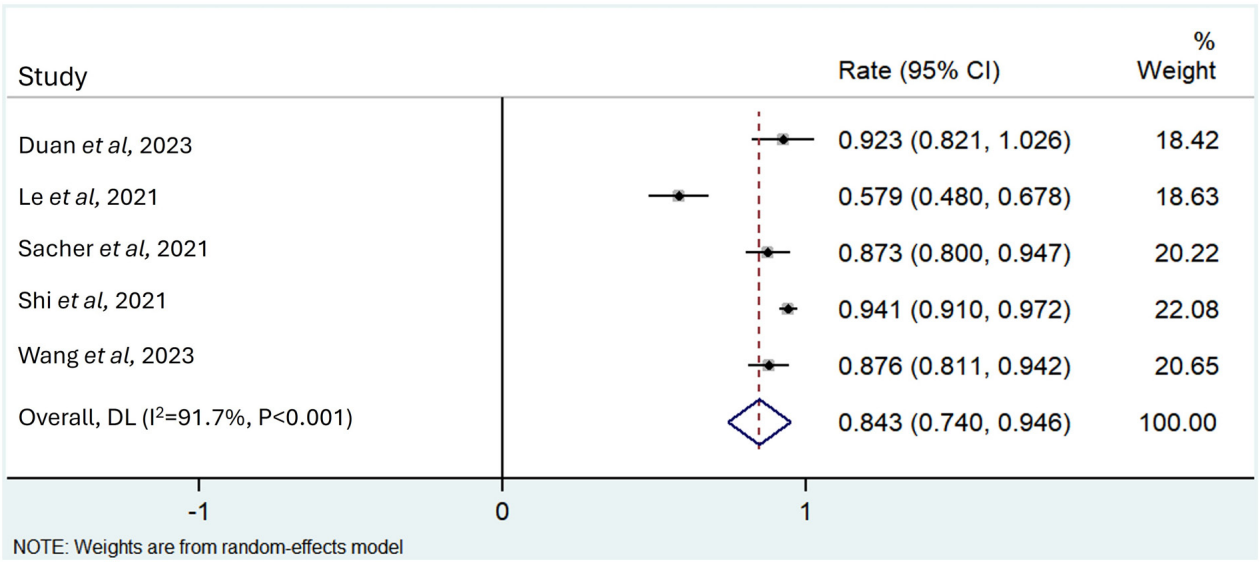

Figure 3. Forest plot of the pooled disease control rate. CI, confidence interval; DL, DerSimonian-Laird procedure.

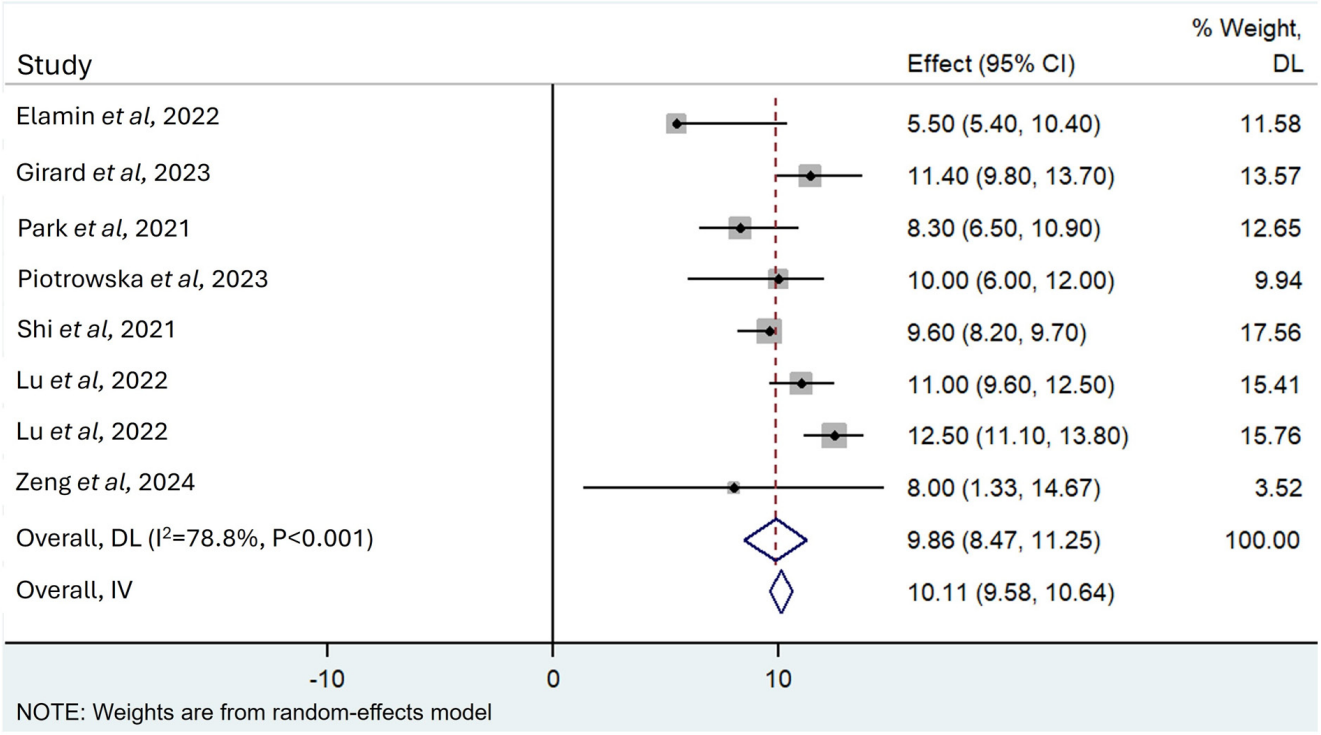

Figure 4. Forest plot of the pooled median progression-free survival. CI, confidence interval; DL, DerSimonian-Laird procedure; IV, inverse variance.

patient population. Therefore, despite the disappointing results observed in mobocertinib trials, third-generation EGFR-TKIs remain a critical treatment strategy for patients with EGFR exon 20 insertion mutations.

EGFR exon 20 insertions are structurally similar to EGFR T790M and tend to be insensitive to first- and second-generation EGFR-TKIs (33). In a previous meta-analysis, only low ORRs (0-9%) were reported for patients with NSCLC exon 20 mutations who were administered first- and second-generation EGFR-TKIs (34). The unsaturated acryloyl group of third-generation EGFR-TKIs forms an irreversible covalent bond with C79, removing the aromatic moiety and potentially solving the spatial site-blocking problem caused by EGFR exon 20 insertions and T790M. However, the oral irreversible third-generation EGFR-TKI, osimertinib, which was developed to be selective for both EGFR sensitizing mutations and EGFR T790M resistance mutations, demonstrated conflicting results in clinical trials (35). The potential antitumour activity of osimertinib was first reported in a small-sample size cohort, where 4/6 patients with NSCLC and an exon 20 insertion mutation receiving 80 mg osimertinib once daily, achieved a partial response and the rest remained stable. The mean

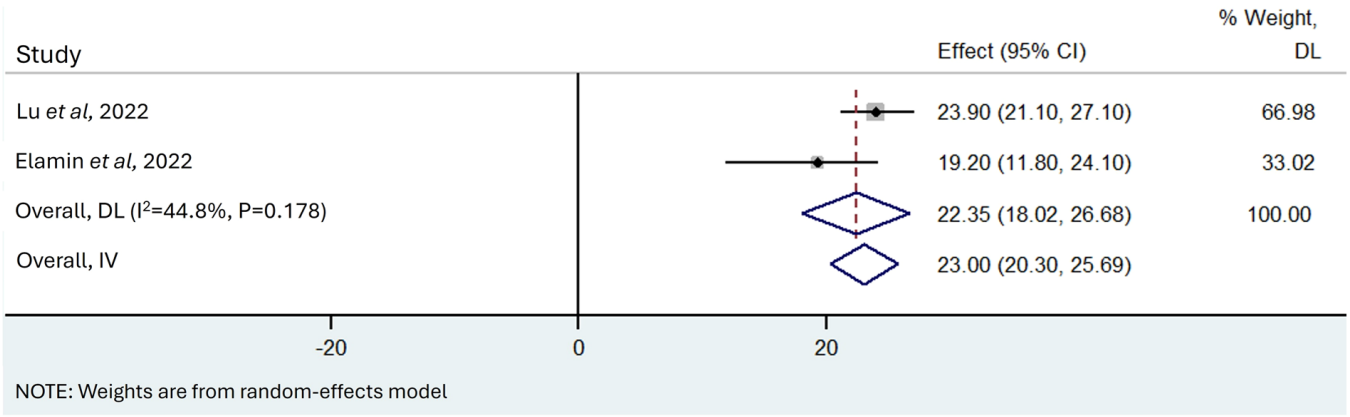

Figure 5. Forest plot of the pooled median overall survival. CI, confidence interval; DL, DerSimonian-Laird procedure; IV, inverse variance.

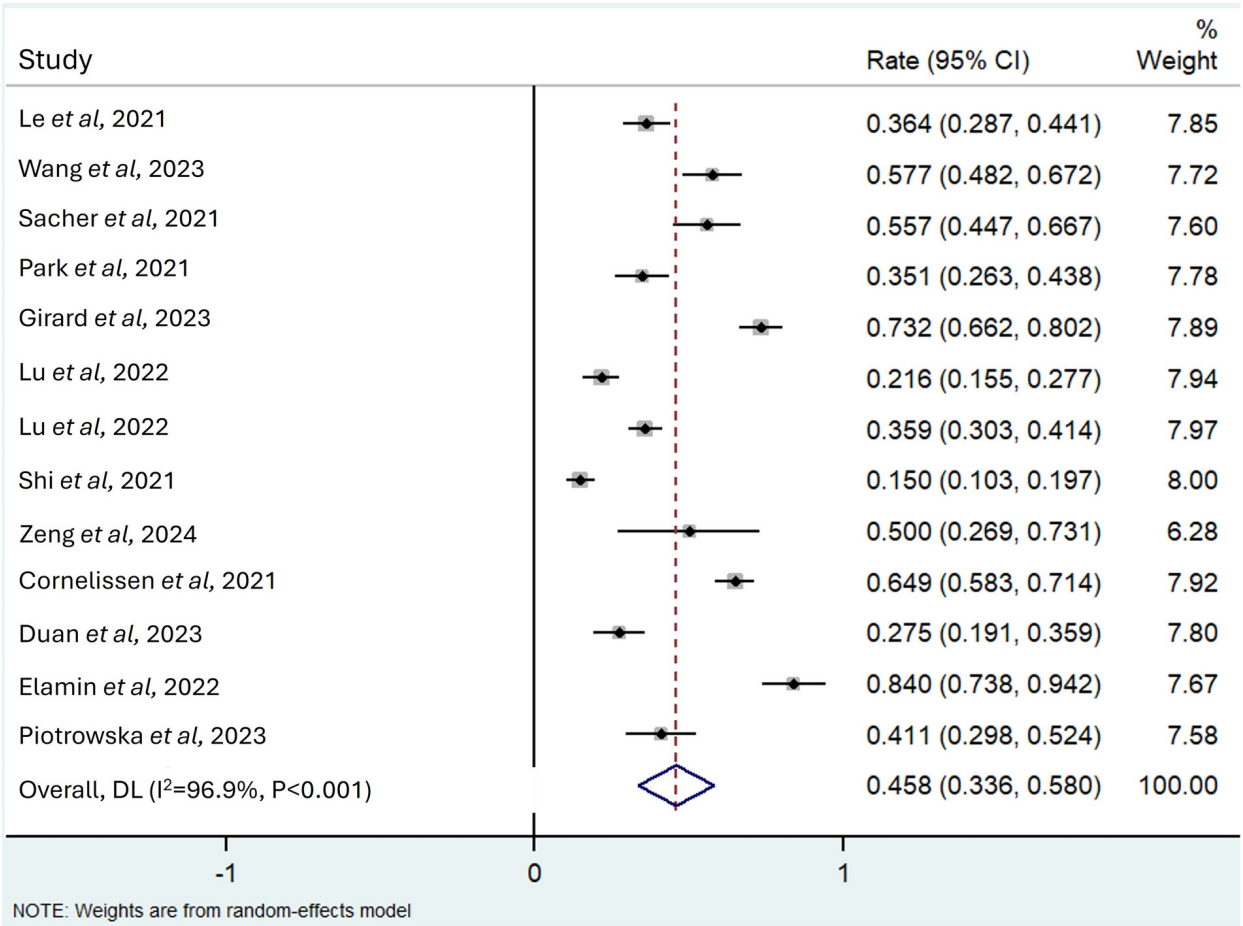

Figure 6. Forest plot of the pooled incidence of treatment relevant adverse events of grade ≥3. CI, confidence interval; DL, DerSimonian-Laird procedure.

PFS was 6.2 months (36). However, in another retrospective analysis with a larger sample size of a Chinese NSCLC cohort harbouring diverse EGFR exon 20 insertions, osimertinib was reported to have little effect, with an ORR of 6.5%, a DCR of 53.2% and a mean PFS of only 2.3 months. Moreover, no dose-response was reported for its use as a first-line treatment or above (7).

Prior to the recent approval of targeted therapies specifically designed for EGFR exon 20 insertion mutations, the cornerstone of treatment strategies for EGFR exon 20 insertion mutations relied on conventional therapies such as traditional EGFR-TKIs, immuno-oncology agents and cytotoxic chemotherapy (37). At present, platinum-based doublet chemotherapy remains the established standard of care for most patients with NSCLC with EGFR exon 20 insertion mutations (38). Real-world evidence has reported that, as a first-line treatment, chemotherapy yields comparable efficacy in EGFR exon 20 insertion mutant NSCLC as in TKI-sensitive EGFR-mutant NSCLC, with an ORR ranging from 19-19.2%, a DCR at 6 months of 41.3%, a median PFS of 6.4-7.6 months and an

Table IV. Pooled incidence of TRAEs of grade ≥3.

TRAEs grade ≥3	Cohorts, n	I^2, %	P-value	Effect (95% CI)
Diarrhoea	10	93.6	<0.001	0.112 (0.060-0.164)
Rash	8	95.1	<0.001	0.124 (0.074-0.173)
Hypokalaemia	5	69.6	0.011	0.027 (0.005-0.049)
Decreased appetite	4	0.0	0.819	0.007 (0.001-0.013)
Anaemia	4	76.7	0.005	0.040 (0.005-0.076)
Vomiting	3	12.3	0.320	0.012 (0.000-0.023)
Thrombocytopenia	3	96.0	<0.001	0.065 (-0.012-0.141)
leukopenia	2	25.6	0.261	0.014 (0.005-0.022)
Headache	2	0.0	0.848	0.008 (0.001-0.015)
Elevated ALT	2	13.1	0.316	0.009 (0.001-0.017)
Elevated AST	2	13.1	0.316	0.009 (0.001-0.017)
Pulmonary embolism	2	87.9	<0.001	0.033 (-0.003-0.068)
Nausea	2	21.2	0.260	0.025 (0.000-0.049)
Dizziness	2	0.0	0.571	0.004 (-0.002-0.010)

TRAEs, treatment relevant adverse events; ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval.

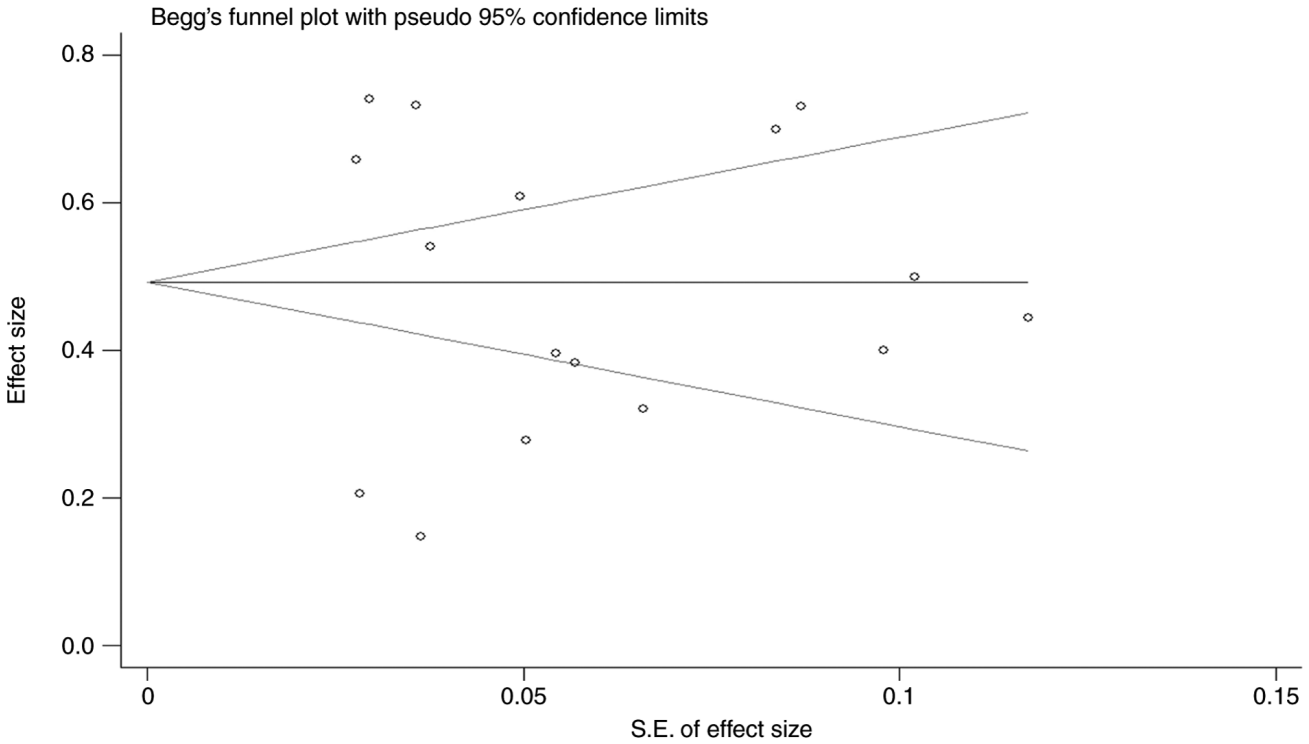

Figure 7. Begg's funnel plot of the objective response rate. S.E., standard error.

OS of 19.9 months (39-42). However, the use of chemotherapy is limited in the clinical setting due to its poorly tolerated side effects. Thus, newer third-generation EGFR-TKIs have been developed (43). In the present meta-analysis, the third-generation EGFR-TKIs included were mostly administered as second line or above treatments. The pooled analysis indicated that the emerging EGFR-TKIs demonstrate a superior treatment outcome for NSCLC with EGFR exon 20 insertions. Although the PFS associated with these TKIs appears slightly suboptimal, it represents a significant improvement over first-line chemotherapy.

In the present study, among the included EGFR-TKIs, poziotinib demonstrated the lowest ORR. Despite being an irreversible pan-human epidermal growth factor receptor (HER) inhibitor with antitumor activity in previously treated patients with NSCLC harbouring HER2 exon 20 insertions in early clinical trials, its ORR and DCR did not outweigh the associated risks, leading to its denial of approval by the FDA (44). The present meta-analysis

drew the same conclusion. Moreover, YK-029A revealed the most favourable ORR of 73.1%, followed by sunvozertinib (60.8%), furmonertinib (60.2%), befotertinib (60.2%) and amivantamab (56.6%). Sunvozertinib, furmonertinib, befotertinib, and amivantamab have now received approval for the treatment of EGFR exon 20 insertion mutant NSCLC (45). YK-029A is an oral irreversible third-generation EGFR-TKI and an analogue of Osimertinib, which is currently being considered as a breakthrough therapeutic option in China for the first-line treatment of advanced EGFR exon 20 insertion mutant NSCLC (46). The present meta-analysis supports their potential as effective treatment options for this condition. However, further real-world data is necessary to supplement the evidence regarding their therapeutic effectiveness compared with standard treatments.

Several limitations should be addressed in the present meta-analysis. Firstly, there was high heterogeneity observed among the included studies. Differences in study design, including sample sizes and follow-up periods, as well as dosing regimens and efficacy profiles of interventions may account for a degree of the heterogeneity. For example, variations in baseline characteristics and how outcomes such as ORR or PFS were measured could influence the pooled results. However, between-study variance was evaluated using random-effects models, ensuring the pooled estimates remained robust despite the heterogeneity. This model assumes that true effect sizes may vary across studies, which provides more conservative estimates and wider confidence intervals, leading to more robust conclusions. By adjusting for study-specific differences, the random-effects model ensures that the results are more generalizable and reflective of real-world variability. Secondly, the lack of sufficient pathological data prevented the analysis of the efficacy of third-generation EGFR-TKIs for different histological types of EGFR exon 20 mutant NSCLC. Thirdly, sensitivity analyses were not performed. Due to the limited number of promising third-generation EGFR TKIs available for analysis at the time of performing the meta-analysis, the number of included studies was relatively small, thus performing sensitivity analyses by removing individual studies would have significantly reduced statistical power without providing additional meaningful insights. Further analysis should be performed when more data from clinical trials are released.

In conclusion, the emerging EGFR-TKIs for patients with NSCLC with EGFR exon 20 insertion mutations have good treatment outcome; however, the PFS outcome appears to be slightly suboptimal. Few studies focused on first-line treatments and the clinical need for this field remains to be elucidated. Further analysis is needed when more new clinical data are released.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KX, JW and DW conceived, designed and planned the study. JW, JJ and ZD performed the literature search and screening. KX, JJ ZD and QH extracted, analysed and interpreted the data. KX, JW and JJ drafted the manuscript. KX and DW confirm the authenticity of all the raw data. All authors critically reviewed the manuscript. KX, JW and DW revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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